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PAIN IS NOT ASSOCIATED WITH COGNITIVE DECLINE IN OLDER ADULTS: A FOUR YEAR LONGITUDINAL STUDY

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ABSTRACT

The potential association between pain and cognitive decline is limited to a few cross-sectional studies, limited in sample size. We therefore aimed to investigate if the presence and severity of pain at baseline could predict a decline in cognitive function over four years of follow-up in the English Longitudinal Study of Ageing. At baseline, participants with no dementia who were “often troubled by pain” were considered to have pain. Pain severity was categorized as mild, moderate, or severe. Cognitive function was explored through verbal fluency (assessed by asking how many different animals the participants could name in 60 seconds), memory (sum of immediate and delayed verbal memory) and processing speed (number of target letters correctly identified on the letter cancellation task). Multivariable linear regression (exposure: pain; outcomes: cognitive change between follow-up and baseline based on standardized residuals) was used. Altogether, 6,515 community-dwelling people with a mean age of 65 years (women=57.3%) were included. Over a 4-year follow-up, after adjusting for 26 potential confounders, no association between pain (yes vs. no) and verbal fluency (beta=0.02; 95%CI: -0.15 to 0.18), memory (0.05; 95%CI: -0.28 to 0.38), or processing speed (0.55; 95%CI: --18.4 to 2.93) at follow-up was found. Only severe pain was associated with greater decline in memory (-0.36; 95%CI: -0.68 to -0.04). In conclusion, in older people, pain was not associated with worsening in cognition, except for severe pain that was marginally associated with worsening in memory tests. Further longitudinal studies are needed to confirm/refute our findings.

Key words: pain; memory; cognitive decline; elderly.

INTRODUCTION

Pain is a frequently reported symptom, with over half of older adults experiencing pain.[1] Pain is associated with a range of adverse outcomes in older age, including a deterioration of activities of daily living, physical and mobility disability[2, 3], low physical activity [4], falls[5], fear of falling[6] and frailty.[7][8] It has been hypothesized that the increased risk for falls and subsequent mobility limitation in older people with pain may partly be attributed to impaired cognition.[9-11]

Whilst research started to consider the impact of pain on cognition in older age, this research has been limited by small samples, studies relying on cross-sectional design, and a small number of tests assessing cognitive functioning.[9-14] Thus, it remains unclear whether pain is associated with various important cognitive subdomains. One recent study using a large cohort of American participants found that persistent pain was associated with a more rapid memory decline and to a mild increase in dementia rate, compared with those without persistent pain.[15] Although this study helps advance our understanding of the link between pain and the onset of poor cognitive status, some important confounders known to influence cognition in older age (such as physical activity[16]) were not assessed. Moreover, only six comorbidities were included, and thus some important causes of pain and/or cognitive decline in the elderly were not considered.[15] Given the high levels of pain in older adults[17] and the need to identify potential modifiable risk factors for cognitive decline, it is important that robust longitudinal research considers this important question.

Given this background, we aimed to explore whether the presence of pain at baseline could predict any decline in several cognitive tests assessed in the English Longitudinal Study of Ageing (ELSA), an ongoing cohort study of community-dwelling older people, over four years of follow-up. In a secondary analysis, we explored whether the severity of pain is associated with declines in cognitive tests.

MATERIALS AND METHODS

The survey

The English Longitudinal Study of Ageing (ELSA) is a nationally representative longitudinal ongoing study of 11,050 people living in England aged 50 and over. The first assessment was conducted in 2002/3 with an extensive nurse visit every four years and a face-to-face interview every two years (http://www.elsa-project.ac.uk/). For the purposes of the present analyses, we used data from wave 2 (2004/2005) (baseline) and wave 4 (2008/2009), since these two waves included all the cognitive tests mentioned below.

Participants gave full informed consent to participate in the study and ethical approval was obtained from the London Multi-center Research Ethics Committee.

Exposure: pain

At baseline (wave 2), participants were asked if they were "often troubled by pain". If they responded "no," their response was coded as "no pain". For those who responded affirmatively, they were asked to evaluate the intensity of their pain on a 3-point scale (mild, moderate, severe).

Outcome variables: changes in cognitive tests

Cognitive function was evaluated in the ELSA through several tests. For the aims of our research, we included three domains of cognition, namely verbal fluency, memory and processing speed.[18] Verbal fluency was assessed by asking how many different animals the participants could name in 60 seconds. Memory was calculated as the sum of immediate and delayed verbal memory. Specifically, to each participant, a list of 10 nouns was presented on a computer, one every 2 s. Participants were asked to recall as many words as possible immediately and again after a short delay during which they carried out the other cognitive tests. As a measure of processing speed, the score of the number of target letters correctly identified on the letter cancellation task was taken. Briefly, for this last task,

participants were given a clipboard to which a page of 780 random letters of the alphabet set out in a grid of 26 rows and 30 columns was attached. The participant was asked to cross out as many target letters (P and W) as possible in 1 min. An example was given at the top of the page to show participants how to cross out the letters. Participants were asked to work across and down the page as if they were reading and to perform the task as quickly and accurately as possible.

To calculate the degree of cognitive change between wave 4 and 2, we carried out a linear regression analysis using the values of each test at wave 2 as independent variables, and scores of cognitive tests at wave 4 as dependent variables and using the standardized residual as a measure of cognitive change.

Other covariates

We considered several potential confounders in the association between pain and cognitive tests, other than age, sex, race, i.e.: (1) education descriptively reported as formal education ("some college" and "college and above") vs. other degrees (no education, high-school, high-school graduate); (2) marital status categorized as married vs. others (not married, divorced, singles, not known); (3) smoking habits as current/former vs. never; (4) disability as having at least one difficulty in activities of daily living (ADL) vs. no difficulty; (5) body mass index (BMI) measured by a trained nurse; (6) self-reported physical activity assessed by questions on the frequency of participation in vigorous, moderate and light physical activities (more than once per week, once per week, one to three times per month, hardly ever) and descriptively reported as high vs. other levels; (7) alcohol consumption categorized as yes vs. no in the last week; (8) depressive symptoms through an 8 item version of the CES-D.[19] (9) household wealth calculated as total net non-pension household wealth, which is a summary measure of the value of financial, physical and housing wealth owned by the household (i.e., a single respondent or a responding couple along with any dependent individuals) minus any debt.

Medical conditions were defined according to whether participants were told by a doctor they had arthritis, osteoporosis, stroke, heart problems (heart attack, congestive heart failure, angina, acute myocardial infarction, arrhythmia), lung diseases (chronic lung disease or asthma), cancer, diabetes, high blood pressure/hypertension, and Parkinson's disease. Information at baseline was used for all the above-mentioned covariates.

Statistical analyses

Normal distributions of continuous variables were tested using the Kolmogorov-Smirnov test. The data were normally distributed and therefore means ± standard deviations (SDs) were used to describe quantitative measures. Percentages were used for all discrete variables. For comparing descriptive characteristics by pain status (yes vs. no), continuous variables were compared using an independent Student's test, whilst a chi-square test was used for categorical variables.

The strength of the association between pain at baseline and cognitive changes occurring between wave 2 and 4 was assessed through a linear regression analysis in two models, one adjusted only for age and sex (basic) and one adjusted for all baseline factors known to be associated with poor cognition and significantly different between people with pain and those without, taking a p-value<0.10 as inclusion criterion for both situations (fully-adjusted multivariable model). Multi-collinearity was assessed with the variance inflation factor (VIF), taking a cut-off of 2 for exclusion, but no covariate was excluded for this reason. The results were reported as betas with their 95% confidence intervals (CIs). We also reported the model's fits as R^2.

In the secondary analyses, we assessed if pain categorized according to its severity (i.e. mild, moderate, severe), could affect cognitive change using a linear regression analysis and reporting as fully-adjusted betas with 95% CIs.

We performed several sensitivity analyses using as potential moderators of our results the median values for continuous variables and the original division for categorical parameters. However, none of the interaction terms between pain and these potential moderators were significant in predicting cognitive tests at follow-up (all p-values >0.05).

All analyses were performed using the SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical analyses were two-tailed, and a p-value <0.05 was assumed to be statistically significant.

RESULTS

Study population

In total, 9,432 participants took part at wave 2, of whom 8,960 had complete data on pain, cognitive function and the covariates. Of these, 8,960 people, we included 6,515 at wave 4 (2,187 were lost during the follow-up, 242 died between the surveys, and 16 participants had a diagnosis of dementia).

The 2,445 participants excluded due to missing cognitive tests at follow-up or since they were dead (wave 4), were significantly older (67.8±11.8 vs. 65.0±9.7 years, $p<0.0001$) than those included (n=6,515). Moreover, the excluded participants were significantly more likely to have pain (42.2 vs. 35.6%, $p<0.0001$) and scored worse in all the cognitive tests assessed at wave 2 ($p<0.0001$ for all comparisons).

Baseline characteristics

The mean±SD age of the 6,515 participants was 65.0±9.7 years (range: 52-90), with a slight majority of women (57.3%) and almost all white (98.1%).

Table 1 shows the baseline characteristics of the 6,515 subjects by absence or presence of pain. Among the 2,317 participants who reported experiencing pain (35.6% of the baseline population), 697 (=10.7% of baseline population), 1,166 (=17.9%) and 450 (=6.9%) reported mild, moderate and severe pain, respectively.

As reported in **Table 1**, those reporting any pain were significantly older and more frequently women ($p<0.0001$ for both comparisons) than the 4,198 individuals not reporting pain at baseline. Moreover, a significant smaller proportion of people with pain reported drinking alcohol in the last week or engaged in a high level of physical activity, such as a higher frequency of smokers and disabled were present (**Table 1**).

The participants with pain had a significantly higher prevalence of all the diseases investigated and reported higher depressive symptoms than those with no pain (**Table 1**). Finally, participants with pain had worse baseline scores in verbal fluency and memory ($p<0.0001$ for both comparisons), but not in processing speed ($p=0.64$) than participants with no pain.

Follow-up data

Of the 2,317 participants experiencing pain 1,492 referred to those who had pain at wave 4 (64.4%), whilst among 4,198 participants that did not report pain at baseline, 852 had pain at wave 4 (20.3%).

Table 2 reports the association between baseline pain and cognitive change between wave 2 and wave 4. After adjusting for 26 potential confounders, no association between pain and change in verbal fluency (0.02 points; 95%CI: -0.15 to 0.18; p=0.85), memory (0.05 points; 95%CI: -0.28 to 0.38; p=0.77) or processing speed (0.55 points; 95%CI: -18.4 to 2.93; p=0.65) was found (**Table 2**). In a sensitivity analysis, we excluded comorbidities at baseline from the models since these can be a mediator in the pathway between pain and cognitive worsening and can potentially attenuate the association between pain and cognition. However, only a slight difference in results was observed in this sensitivity analysis and pain was not significantly associated with change in verbal fluency (-0.009 points; 95%CI: -0.33 to 0.31; p=0.95), memory (-0.02 points; 95%CI: -0.18 to 0.15; p=0.85) or processing speed (-2.21 points; 95%CI: -7.85 to 4.25; p=0.57) (other details not shown)..

Table 3 shows the association of pain (categorized according to its severity as mild, moderate or severe) and cognitive changes between wave 2 and 4. Taking people with no pain as reference and after adjusting our analyses for all the confounders mentioned before, the severity of pain was not associated with decrease in any cognitive tests with the exception of memory where severe pain was associated with decline in memory (-0.36 points; 95%CI: -0.68 to -0.04; p=0.04).

DISCUSSION

In this study, involving a large sample of community dwelling older people, we found that pain was associated with poorer performance on some cognitive tests cross-sectionally (at baseline), but not with significant changes in these scores after four years of follow-up. We also found that after adjustment for many potential confounders, previously significant associations disappeared.

Previous literature reports that pain could be associated with cognitive dysfunction through several mechanisms. In a pivotal review regarding this issue[20], the authors reported that pre-clinical and clinical studies suggest three theories, i.e. (1) competing limited resources, (2) neuroplasticity and (3) dysregulated neurochemistry. Regarding the first point, it was hypothesized that pain may compete with other attention-demanding stimuli for limited cognitive resources.[21] Thus, the presence of pain stimuli may impair top-down attentional control mechanisms which filter out task-irrelevant stimuli resulting in impaired task performance. [21] Regarding the second point, as shown by neuroimaging studies, pain seems to be associated with a reduction of grey matter in insular cortex and in neurogenesis in hippocampus, two key structures for cognition.[21] Third, pain seems to be associated with an imbalance in several neurotransmitters, in particular a reduction in brain derived neurotrophic factor (BDNF)[22], an increase in glutamate inhibitor pathway[23] and in GABA signaling[24] leading to a reduction in cognitive function. However, other factors such as the use of analgesic medications are probably important in explaining the association between pain and cognitive function.[20]

Our results are in contrast with some previous literature on the relationship between pain and any worsening in cognitive function. Several cross-sectional studies reported a significant association between pain and cognitive function.[9-14] A large recent longitudinal study involving a sample of more than 10,000 participants followed up for 10 years reported that pain at baseline was associated with an accelerated memory decline and increased risk for dementia.[15] A number of hypotheses

can explain the differences between our research and previous papers. First, and probably more important, is the number and type of covariates used for adjusting the analyses. Indeed, we adjusted for 26 potential confounders including physical comorbidities associated with pain, such as osteoporosis[25], arthritis[26], or cancer[27], which seem to be associated with poor cognitive performance, whilst previous studies adjusted only for some of these confounders. Thus, it is difficult to state whether pain *per se* or the comorbidities associated with pain are the risk factors for cognitive decline. However, a sensitivity analysis excluding comorbidities from the models showed that that results were largely unchanged. Second, the tests used for assessing cognitive function in previous papers were different from those used here. Third, compared to the largest work regarding this topic [15], we found a difference of about 8 years between our and this study that can further influence our results. It is possible that results would have been different if we had used different cognitive function tests or if the follow-up time was longer. Finally, there may be an element of survival bias, where we excluded a considerable portion of people due to missing data at follow up, who may have had worse cognitive function at baseline and higher prevalence of pain. Unfortunately, during the course of longitudinal follow-up studies, many older participants dropout. When dropout is dependent on unknown or unmeasured parameters (as in our study), there is no easy solution for bias correction. [28] Thus, it is important to highlight that our results may be biased by this high rate of dropouts during follow-up period.

Severe pain at baseline was associated with declines in memory test scores assessed through immediate and delayed word recall. However, the result was only marginally significant. Thus, this result should be interpreted with caution. The literature so far in both clinical and pre-clinical settings, in fact, reported that pain reduced all the aspects of cognitive function, including those assessed in our study (verbal fluency, memory and processing speed) and others (such as general cognition assessed through common tests like the mini-mental state examination).[9-15] However, the different tests used to assess cognitive function in previous studies and ours make direct comparisons difficult.

Further studies are needed to assess whether our results can be replicated, and whether severe pain is more likely to be associated with cognitive decline in some domains (e.g., memory) than others.

The findings of our study should be interpreted within their limitations. First, more than 3,000 participants were lost to follow-up. These individuals were older and were more likely to have pain and perform poorly on cognitive tests. Thus, attrition bias may exist. It is also possible that people experiencing more pain at wave 2 died before showing any decrease in cognitive tests (survival bias). Second, pain was assessed only through two questions retrospectively and information on the site of pain, the use of antalgics or its chronicity were not collected while sophisticated tools for assessing pain (e.g. numerical rating scale) were not used. Third, due to the observational nature of our study, we cannot deduce the exact direction of effect of our findings. Finally, cognitive ability test scores in older people may reflect not only a possible decline, but also their peak prior cognitive ability[28], but we did not have any information regarding the trajectories of their cognitive function during the lifespan.

In conclusion, our large study involving older community-dwelling participants suggests that cognitive decline may be more pronounced among those with pain, but only due to the presence of factors associated with both pain and poor cognition. Since pain could be treated with medications and other interventions, further studies are needed to better understand the association between pain and cognition in the elderly.

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Data are available from the UK Data Service for researchers who meet the criteria for access to confidential data. Data are from waves 2 and 4 of the English Longitudinal Study of Ageing (ELSA). Data and contact details may be obtained via the website http://www.adls.ac.uk/find-administrative-data/linked-administrative-data/english-longitudinal-study-of-ageing/

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Table 1. Baseline characteristics by presence or absence of pain.

Variable	Pain (+) (n=2317)	Pain (-) (n=4198)	p-value
General characteristics			
Age (years)	65.5 (9.5)	64.2 (9.7)	<0.0001
Females (%)	53.7	63.7	<0.0001
College and above (%)	17.1	9.3	<0.0001
Married (%)	68.3	66.0	0.06
Alcohol drinking (%)	28.8	35.1	<0.0001
Present/previous smokers (%)	60.0	64.8	<0.0001
High physical activity level (%)	24.3	14.9	<0.0001
Disabled (%)	36.0	7.8	<0.0001
Whites (%)	98.6	97.3	0.001
Household wealth (£)	235,485±391,888	321,455±461,741	<0.0001
Body mass index (Kg/m^2)	29.1 (5.5)	27.4 (4.5)	<0.0001
Medical conditions			
Angina (%)	14.1	6.8	<0.0001
Myocardial infarction (%)	7.1	4.5	0.001
Heart failure (%)	1.8	0.7	0.007
Arrhytmia (%)	12.3	6.7	<0.0001
Arthritis (%)	65.0	25.4	<0.0001
Osteoporosis (%)	12.1	4.1	<0.0001
Stroke (%)	5.7	4.2	<0.0001
Parkinson's disease (%)	0.6	0.4	0.21
Lung disease (%)	10.8	4.7	<0.0001

Variable	Pain (+) (n=2317)	Pain (-) (n=4198)	p-value
Asthma (%)	12.5	11.1	<0.0001
Cancer (%)	7.9	6.9	0.20
Diabetes (%)	11.2	7.0	<0.0001
High blood pressure (%)	52.5	38.1	<0.0001
CESD (points)	2.2 (2.2)	1.1 (1.6)	<0.0001
Cognitive tests (at wave 2)			
Verbal fluency	19.7 (6.4)	21.0 (6.5)	<0.0001
Memory	9.9 (3.7)	10.6 (3.5)	<0.0001
Processing speed	294 (105)	296 (98)	0.64

Notes: Numbers are mean (standard deviations) or percentages as appropriate.

Abbreviations: CESD: Center for Epidemiologic Studies Depression.

Table 2. Association between baseline presence of pain and change in scores of cognitive tests between wave 4 and 2.

	Sample size	*Basic-adjusted beta (95%CI)*	*p – value*	*R^2*	*Fully-adjusted beta (95%CI)*	*p – value*	*R^2*
Verbal fluency	6440	0.73 (0.52-0.93)	<0.0001	0.10	0.02 (-0.15; 0.18)	0.85	0.51
Memory	6440	1.43 (1.04-1.82)	<0.0001	0.10	0.05 (-0.28; 0.38)	0.77	0.48
Processing speed	6515	-1.50 (-3.73; 0.72)	0.19	0.00	0.55 (-18.4; 2.93)	0.65	0.19

Notes:

Unless otherwise specified, data are presented as betas and their 95% confidence intervals, using the standardized residuals at wave 4 as outcome.

In all the elaborations, those with no pain at baseline were taken as reference.

Basic-adjusted model included age (as continuous) and gender; fully-adjusted model includes, other than age and sex, baseline values of: race; educational level (as continuous variable); marital status (married vs. others); household wealth; activities of daily living score; CES-D score; body mass index; smoking habits (present/former vs. never); physical activity level; alcohol drinking (yes vs. no); presence at baseline of angina, myocardial infarction, heart failure, arrhythmia, stroke, arthritis, osteoporosis, Parkinson's disease, lung disease, asthma, cancer, diabetes, high blood pressure (all yes vs. no); cognitive test values at wave 2.

Table 3. Association between baseline severity of pain and change in scores of cognitive tests between wave 4 and 2.

	No pain (n=4,198)	*Mild pain (n=697)*	*p-value*	*Moderate pain (n=1,166)*	*p-value*	*Severe pain (n=450)*	*p-value*
Verbal fluency	Reference	0.07 (-0.38; 0.53)	0.75	-0.18 (-0.58; 0.23)	0.39	0.06 (-0.57; 0.69)	0.85
Memory	Reference	0.02 (-0.22; 0.25)	0.89	0.05 (-0.16; 0.26)	0.63	-0.36 (-0.68; -0.04)	0.04
Processing speed	Reference	3.02 (-6.55; 12.59)	0.54	-0.08 (-8.53; 8.38)	0.99	0.82 (-12.32; 13.95)	0.90

Notes:

Unless otherwise specified, data are presented as fully-adjusted betas and their 95% confidence intervals, using the standardized residuals at wave 4 as outcome.

In all the elaborations, those with no pain at baseline were taken as reference.

Fully-adjusted model includes: age (as continuous); gender; race; educational level (as continuous variable); marital status (married vs. others); household wealth; activities of daily living score; CES-D score; body mass index; smoking habits (present/former vs. never); physical activity level; alcohol drinking (yes vs. no); presence at baseline of angina, myocardial infarction, heart failure, arrhythmia, stroke, arthritis, osteoporosis, Parkinson's disease, lung disease, asthma, cancer, diabetes, high blood pressure (all yes vs. no); cognitive test values at wave 2.